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Predictors of follow-up and assessment of selection bias from dropouts using inverse probability weighting in a cohort of university graduates

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Abstract. Dropouts in cohort studies can introduce selection bias. In this paper, we aimed (i) to assess predictors of retention in a cohort study (the SUN Project) where participants are followed-up through biennial mailed questionnaires, and (ii) to evaluate whether differential follow-up introduced selection bias in rate ratio (RR) estimates. The SUN Study recruited 9907 participants from December 1999 to January 2002. Among them, 8647 (87%) participants answered the 2-year follow-up questionnaire. The presence of missing information in key variables at baseline, being younger, smoker, a marital status different of married, being obese/overweight and a history of motor vehicle injury were associated with being lost to follow-up, while a self-reported history of cardiovascular disease predicted a higher retention proportion. To assess whether differential follow-up affected RR estimates, we studied the association between body mass index and the risk of hypertension, using inverse probability weighting (IPW) to adjust for confounding and selection bias. Obese individuals had a higher crude rate of hypertension compared with normoweight participants (RR = 6.4, 95% confidence interval (CI): 3.9–10.5). Adjustment for confounding using IPW attenuated the risk of hypertension associated to obesity (RR = 2.4, 95% CI: 1.1–5.3). Additional adjustment for selection bias did not modify the estimations. In conclusion, we show that the follow-up through mailed questionnaires of a geographically disperse cohort in Spain is possible. Furthermore, we show that despite existing differences between retained or lost to follow-up participants this may not necessarily have an important impact on the RR estimates of HTN associated to obesity.

Key words: Attrition, Body mass index, Cohort studies, Hypertension, Inverse probability weighting, Selection bias

Abbreviations BMI = body mass index; CI = confidence interval; HTN = hypertension; IPW = inverse probability weighting; MET = metabolic equivalent; RR = rate ratio; SUN = Seguimiento Universidad de Navarra

Introduction

Selection bias has been considered an especially serious drawback in case-control studies, but this problem can also afflict cohort studies. In the latter study design, selection bias may arise from three mechanisms: (i) unwillingness to participate, (ii) missing information in some covariates (and thus, exclusion from some analyses) and (iii) attrition of the cohort (dropouts or losses to follow-up) [1, 2]. Dropouts can lead to selection bias because individuals who do not respond in the follow-up tend to be different from respondents [3]. This can be the case particularly if the exposure of interest is associated with censoring and there are variables associated both with the study outcome and with censoring [4].

A first step in the study of a possible selection bias introduced by cohort attrition is to compare the characteristics of respondents and non-respondents. Afterwards, different tools can be used to explore the magnitude of bias and to correct it [5]. A recently proposed approach to adjust for selection bias is inverse probability weighting (IPW) [4, 6]. This method works by creating a pseudopopulation, in which uncensored individuals are weighted by the inverse of the probability of being non-censored given past exposure and past levels of potential confounding variables. In this way, the study participant accounts in the analysis for those with similar characteristics that were not selected (because they were censored).

Cohort studies can have a variety of designs. Some are based in geographically dispersed populations

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with special characteristics and their participants are usually followed-up through mailed questionnaires. This is an efficient way to carry out large prospective studies. However, most of these studies are being conducted in the United States [7–9], and there is no information about the follow-up of cohorts with these characteristics in Europe. Also, given the difficulty to track cohort participants exclusively through mail [10], it is valuable to assess factors associated with dropping out from the study.

The *Seguimiento Universidad de Navarra* (SUN, University of Navarra Follow-Up) Study was established in 2000 in Spain [11]. Participants in this cohort are all university graduates, recruited and followed-up through biennial mailed questionnaires. The objective of this paper was twofold: (i) to describe the initial follow-up of the SUN cohort and (ii) to investigate whether losses to follow up introduced bias in our estimations. For this latter objective, we studied the potential bias due to differential follow-up with a particular example, the association between body mass index (BMI) at baseline and the risk of incident hypertension (HTN) using IPW.

Methods

The SUN Study

The SUN Study is a multipurpose, dynamic cohort of university graduates in Spain. The SUN Study was approved by the Institutional Review Board of the University of Navarra. Among its objectives are the study of the association between dietary and other lifestyle variables and the incidence of cardiovascular disease, hypertension, obesity, and diabetes, and the assessment of risk factors for motor-related injuries. Its methods have been described previously [11]. Briefly, beginning on December 1999, all university graduates from the University of Navarra, and university graduates from some professional associations received a letter of invitation to participate in the study, a questionnaire to respond and a postage-prepaid envelope to return the questionnaire. This baseline questionnaire gathered information about sociodemographic variables, lifestyle factors, including physical activity, clinical variables and included a detailed food frequency questionnaire previously validated in Spain [12]. To quantify the volume and intensity of leisure-time physical activity, we calculated an activity metabolic equivalent (MET) index for each participant. We assessed each participant's involvement and time spent in 17 different activities. We assigned a multiple of the resting metabolic rate (MET score) to each of these activities using previously published guidelines [13]. The MET score of each activity was multiplied by the weekly time spent in each activity and a value of overall weekly MET-hours was obtained.

Follow-up of the cohort

In the baseline questionnaire, we requested three postal addresses from each participant (main address, alternative personal address, and name and address of a relative or friend) and at least one e-mail address.

The follow-up is conducted through biennial mailed questionnaires. Once a participant reaches its second (or fourth, or sixth) anniversary from the reception of the baseline questionnaire, we send him/her a follow-up questionnaire. To ensure high retention rates, we send up to five reminders to non-respondents, the last of which is mailed-certified. In the non-questionnaire year (i.e., first, third, etc.), a salutatory letter is sent to all participants reminding them of the importance of continuous collaboration and the need to update their addresses.

Participants can contact the study investigators through email, telephone and postal address. Interestingly, e-mail has been an important and inexpensive mean to reach some participants and to communicate with them. Internet-based tools have been introduced to both update addresses and answer questionnaires.

In this paper we included all participants recruited up to January 2002 who answered the 2-year follow-up questionnaire before 25 July 2004.

Evaluation of bias: association between BMI and incident HTN

To assess the impact of selection bias introduced by losses to follow-up, we studied the association between BMI in the baseline questionnaire, a classical cardiovascular risk factor, and the risk of incident HTN as assessed in the 2-year follow-up questionnaire. We decided to study this association because, first, BMI was associated with the probability of retention in our study population and, two, because it is a well-known risk factor for HTN. BMI was computed as the ratio between baseline self-reported weight in kilograms divided by squared self-reported height (in meters). The repeatability and validity of self-reported weight have been the objective of a previous publication [14]. There, we showed that the mean relative error in self-reported weight was 1%. Also, we assessed the validity of the self-reported diagnosis of HTN in a random sample of 79 individuals reporting a medical diagnosis of HTN and 41 not reporting such diagnosis living in the metropolitan area of Pamplona (Navarra, Spain). These participants were representative of the SUN study population. Two study physicians performed two blood pressure measurements and an interview with these participants. The mean of both blood pressure measurements was computed to define hypertensive status. We defined HTN as systolic blood pressure ≥140, or diastolic blood pressure ≥90, or taking anti-HTN medication. Using this definition, the positive

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and negative predictive value for the self-reported diagnosis of HTN were 82 and 85%, respectively. A detailed description of this validation study has been published elsewhere [15].

For this particular evaluation we excluded otherwise eligible individuals who reported HTN, cardiovascular disease, cancer or diabetes at baseline, those with missing values in any covariate of interest, and those with extremely low or high caloric intakes at baseline (lower than 400 or higher than 3500 kcal/day for women, and lower than 600 or higher than 4200 kcal/day for men). We consider as potential confounding factors those variables previously reported to be determinants of the incidence of HTN (age, sex, physical activity, alcohol intake, fruit and vegetable consumption), markers of a healthier lifestyle (smoking), and variables we found associated with dropout probability (marital status).

Statistical analysis

To attain the first objective, description of the follow-up of the cohort, we compared respondents and non-respondents to the first follow-up questionnaire using logistic regression. The outcome was non-response to the follow-up questionnaire, and as independent candidate predictors we studied variables previously associated to dropout in other studies, such as different sociodemographic variables, and risk factors for cardiovascular disease, HTN, and motor vehicle injuries (the main outcomes of interest in the SUN study). Continuous variables were categorized for all the analyses. Initially we ran univariate logistic regression models for each independent variable. Then, we ran a multivariate model simultaneously including every variable considered in the univariate analysis. In this analysis, we excluded individuals with missing values in any variable to allow the model to run properly. Goodness-of-fit was assessed with the Hosmer-Lemeshow test.

For the second aim of the study, we used a marginal structural Cox proportional hazards models to study the association between BMI and incidence of HTN [16], using IPW to adjust for confounding and selection bias related to losses to follow-up. In these models, we categorized the BMI as lower than 25 kg/m^2, from 25 through 30 kg/m^2, and greater than 30 kg/m^2 [17].

The use of IPWs in a marginal structural model allows the estimation of causal effects in the population, under the assumption of conditional exchangeability [4, 6, 16]. For a formal definition of causal effects and an explanation of the assumption of conditional exchangeability in observational studies see, for example, [18] and [6]. Briefly, we say that an exposure E has a causal effect in a population if the proportion of subjects developing a disease D had everybody in the population been exposed to E is different to the proportion of subjects developing that disease had everybody been unexposed. In other words, the exposure E has a causal effect if there is a difference between the counterfactual risk of the outcome D had everybody been exposed and the counterfactual risk everybody had not been exposed. By conditional exchangeability we mean that, after conditioning on potential confounders, we can assume that the probability of having a disease D had everybody been exposed to E or had they been unexposed is independent of the actual exposure status, i.e. in every level of potential confounders the exposure E can be assumed to be assigned randomly. That is, conditional exchangeability implies that exposed and unexposed individuals are exchangeable across levels of potential confounders.

The IPW method to adjust for confounding works by creating a pseudopopulation where each individual in the population is weighted by the inverse of the conditional probability of receiving the exposure that she or he received (conditional to the actual values of the confounding variables). In that pseudopopulation there is no confounding for the variable used to condition for when calculating the weights, under the assumption of no residual confounding.

To adjust for confounding, we computed stabilized weights for each individual included in the final analysis as the ratio of the probability of being in the corresponding BMI category over the probability of being in the observed BMI category for an individual given her or his distribution of potential confounders (Equation 1). Stabilized weights tend to be much less variable than standard weights (as defined in the previous paragraph) [16]. The numerator probability could be computed directly from the data, as the proportion of individuals in each BMI category. The denominator was estimated using ordinal logistic regression. We computed rate ratios (RR) using weighted Cox proportional hazard models. Confidence intervals were calculated using robust (or sandwich) estimators of the variance. The use of robust estimators of the variance is recommended in this case because the ordinary Wald confidence intervals will not be guaranteed to provide at least 95% coverage probability [16].

$$SW = \frac{f(\text{BMI})}{f(\text{BMI}|\text{age, sex, physical activity, alcohol, smoking, fruit \& vegetable consumption, marital status})} \quad (1)$$

To adjust for selection bias, we computed another set of stabilized weights, with the probability of being non-censored given BMI in the numerator, and the

probability of being non-censored, given BMI and other variables associated with censoring status and the outcome (Equation 2; C = 0 for those non-censored) [4]. The numerator could be computed directly from the data as the retention proportion by BMI categories. The denominator was computed with a logistic regression with non-censoring as the outcome and factors associated to censoring as independent variables.

$$SW' = \frac{f(C=0|\text{BMI})}{f(C=0|\text{BMI, age, sex, physical activity, alcohol, smoking, fruit \& vegetable consumption, marital status})} \quad (2)$$

The final model used weights computed as the product of the stabilized weights for confounding adjustment times the stabilized weights for selection bias adjustment.

$$\text{Finalweights} = SW' \times SW \quad (3)$$

In the absence of unmeasured confounding, unmeasured informative censoring, and model misspecification, the use of final weights (Equation 3) creates a pseudopopulation that corrects both selection bias and confounding [19]. Analyses were performed with SAS version 9 (SAS Institute, Cary, NC, USA). Weighted Cox proportional hazard models were run using the WEIGHT statement, and the COVS options in the PROC PHREG statement.

Finally, to assess if selection bias depended on the main exposure of interest, we repeated the IPW analysis to analyze the association between age at baseline (categorized as < 25, 25–34, 35–44, ≥45 years) and the risk of HTN. Models to compute weights included the same variables as in the BMI case.

Results

At the time of the analysis, 8647 of the 9907 eligible to have submitted their 2-year follow up questionnaire had done so (87%). Table 1 shows some characteristics of respondents and non-respondents to the follow-up questionnaire. In general, non-respondents had a higher proportion of individuals with missing values at the baseline questionnaire for all variables considered. Among non-respondents, age and fruit and vegetable consumption were lower, whereas the proportion of smokers, of non-married participants and of those without prior history of disease was higher.

In the univariate logistic regression analysis (Table 1) being younger, non-married, smoker, not having a driver's license and having suffered a previous motor vehicle accident with hospitalization were associated with a higher probability of attrition. On the other hand, a previous history of cardiovascular disease or hypercholesterolemia at baseline increased the probability of responding the 2-year follow-up questionnaire. Having a missing value in the baseline questionnaire in any item was associated with a higher probability of attrition.

When we adjusted simultaneously for all the variables shown in Table 1, a younger age, being non-married, smoker, obese, having a history of motor vehicle accident with hospitalization and an absence of previous history of cardiovascular disease or injury were associated with a higher probability of attrition. The Hosmer-Lemeshow did not indicate a statistically significant lack of fit of our model. Only 3% of our sample would be misclassified in the contingency table, which is used to compute the Hosmer-Lemeshow test (comparing observed versus expected counts across deciles of the predicted probability).

To study the association between BMI and the risk of HTN, from the initial 9907 study participants, 3321 participants were excluded due to either having prevalent HTN, cardiovascular disease, cancer or diabetes, their reporting of extreme caloric intakes or presenting missing values in some variables. That left 6686 for the analysis, 5880 (88%) of whom had submitted their first follow-up questionnaire. There were 180 new cases of HTN during 13,526 person-years of follow-up. In Table 2, we show the rate ratios of HTN according to BMI categories. In the crude analysis, BMI was associated with an important increase in the risk of HTN. When we adjusted using IPW, the risk ratio estimates were attenuated but still showed an important direct association between BMI and the risk of HTN. Age and sex were the variables that accounted for most of the change in the risk ratios between crude and multivariate estimations. Additional adjustment for selection bias did not substantially change the risk ratio estimates. We repeated the IPW analysis considering age as the main exposure, and we did not observe an important effect of censoring due to dropout in the estimates (data not shown).

Discussion

In this assessment of the first 2-years follow-up of the first 10,000 participants of the SUN cohort, we show that, as it happens with similar cohorts in the US, follow-up through mailed questionnaires of a highly educated cohort in Spain is feasible. Comparable populations in other European countries could be a valuable setting to conduct studies with similar design. We also show that individuals who were lost to follow-up were different than those

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Table 1. Baseline characteristics of the first 9907 participants in the SUN cohort by respondent status to the 2-year follow-up questionnaire, and odds ratios and 95% confidence intervals of loss to follow-up according to these characteristics

	Respondents (n = 8647)*	Non-respondents (n = 1260)*	Total (n = 9907)	Crude OR	Adjusted OR[a]
Sociodemographic variables					
Age					
< 25	1363 (83.1)	277 (16.9)	1640	1 (ref.)	1 (ref.)
25–34	2970 (86.1)	481 (13.9)	3451	0.8 (0.7–0.9)	0.8 (0.7–1.0)
35–44	2088 (92.1)	180 (7.9)	2268	0.4 (0.3–0.5)	0.5 (0.4–0.7)
≥45	2201 (89.5)	259 (10.5)	2460	0.6 (0.5–0.7)	0.5 (0.4–0.7)
Missing	25 (28.4)	63 (71.6)	88	12.4 (7.7–20.1)	N/A
Gender					
Female	5131 (87.1)	761 (12.9)	5892	1 (ref.)	1 (ref.)
Male	3439 (88.0)	469 (12.0)	3908	0.9 (0.8–1.0)	1.0 (0.9–1.2)
Missing	77 (72.0)	30 (28.0)	107	2.6 (1.7–4.0)	N/A
Marital status					
Married	4131 (90.0)	46 (10.0)	4592	1 (ref.)	1 (ref.)
Single	4060 (85.3)	701 (14.7)	4761	1.5 (1.4–1.8)	1.1 (1.0–1.3)
Widowed	98 (81.0)	23 (19.0)	121	2.1 (1.3–3.3)	2.4 (1.4–3.9)
Separated/divorced/others	197 (83.8)	38 (16.2)	235	1.7 (1.2–2.5)	1.7 (1.2–2.6)
Missing	161 (81.3)	37 (18.7)	198	2.1 (1.4–3.0)	N/A
Lifestyle factors					
Physical activity[b]					
Sedentary	1863 (86.0)	303 (14.0)	2166	1 (ref.)	1 (ref.)
Less active	2268 (87.5)	324 (12.5)	2592	0.9 (0.7–1.0)	1.0 (0.8–1.2)
Moderately active	2379 (88.7)	303 (11.3)	2682	0.8 (0.7–0.9)	0.8 (0.7–1.0)
Very active	2062 (87.2)	303 (12.8)	2365	0.9 (0.8–1.1)	1.0 (0.8–1.2)
Missing	75 (73.5)	27 (26.5)	102	2.2 (1.4–3.5)	N/A
Smoking					
Never smoker	3824 (87.9)	528 (12.1)	4352	1 (ref.)	1 (ref.)
Past smoker	2226 (88.9)	279 (11.1)	2505	0.9 (0.8–1.1)	1.1 (0.9–1.3)
Current smoker	2226 (85.2)	386 (14.8)	2612	1.3 (1.1–1.4)	1.3 (1.1–1.5)
Missing	371 (84.7)	67 (15.3)	438	1.3 (1.0–1.7)	N/A
Use of seatbelt					
Always	7085 (87.3)	1028 (12.7)	8113	1 (ref.)	1 (ref.)
Not always	1240 (88.8)	157 (11.2)	1397	0.9 (0.7–1.0)	0.9 (0.8–1.1)
Almost never	168 (84.0)	32 (16.0)	200	1.3 (0.9–1.9)	1.1 (0.7–1.7)
Missing	154 (78.2)	43 (21.8)	197	1.9 (1.4–2.7)	N/A
Use of alcohol and driving					
Never	3748 (87.2)	550 (12.8)	4298	1 (ref.)	1 (ref.)
Almost never	1506 (88.4)	197 (11.6)	1703	0.9 (0.8–1.1)	0.9 (0.7–1.1)
Sometimes	2456 (89.0)	303 (11.0)	2759	0.8 (0.7–1.0)	0.8 (0.7–1.0)
Do not know how to drive	775 (82.2)	168 (17.8)	943	1.5 (1.2–1.8)	1.3 (1.1–1.6)
Missing	162 (79.4)	42 (20.6)	204	1.8 (1.2–2.5)	N/A
Alcohol consumption (g/day)					
Non-drinker	2011 (87.9)	278 (12.1)	2289	1 (ref.)	1 (ref.)
Drinker					
< 3 g/d	2476 (87.7)	346 (12.3)	2822	1.0 (0.9–1.2)	1.1 (0.9–1.3)
3–12 g/d	2689 (86.9)	406 (13.1)	3095	1.1 (0.9–1.3)	1.1 (0.9–1.4)
≥12 g/d	1397 (87.3)	203 (12.7)	1600	1.1 (0.9–1.3)	1.2 (1.0–1.5)
Missing	74 (73.3)	27 (26.7)	101	2.6 (1.7–4.2)	N/A
Fruit and vegetable consumption					
Below median	4252 (86.7)	652 (13.3)	4904	1 (ref.)	1 (ref.)
Above median	4321 (88.1)	581 (11.9)	4902	0.9 (0.8–1.0)	0.9 (0.8–1.0)
Missing	74 (73.3)	27 (26.7)	101	2.4 (1.5–3.7)	N/A
Fat (% energy intake)					
Below median	4292 (87.4)	617 (12.6)	4909	1 (ref.)	1 (ref.)
Above median	4273 (87.4)	614 (12.6)	4887	1.0 (0.9–1.1)	0.9 (0.8–1.0)
Missing	82 (73.9)	29 (26.1)	111	2.5 (1.6–3.8)	N/A
Protein (% energy intake)					
Below median	4243 (87.6)	598 (12.4)	4841	1 (ref.)	1 (ref.)

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Table 1. Continued

	Respondents (n = 8647)*	Non-respondents (n = 1260)*	Total (n = 9907)	Crude OR	Adjusted OR[a]
Above median	4322 (87.2)	633 (12.8)	4955	1.0 (0.9–1.2)	1.1 (1.0–1.2)
Missing	82 (73.9)	29 (26.1)	111	2.5 (1.6–3.9)	N/A
Clinical variables					
BMI (kg/m2)					
< 25	5962 (87.4)	856 (12.6)	6818	1 (ref.)	1 (ref.)
25–30	1962 (87.8)	273 (12.2)	2235	1.0 (0.8–1.1)	1.1 (1.0–1.4)
> 30	363 (84.8)	65 (15.2)	428	1.2 (0.9–1.6)	1.5 (1.1–2.0)
Missing	360 (84.5)	66 (15.5)	426	1.3 (1.0–1.7)	N/A
Cardiovascular disease					
No	8264 (87.1)	1225 (12.9)	9489	1 (ref.)	1 (ref.)
Yes	383 (91.6)	35 (8.4)	418	0.6 (0.4–0.9)	0.6 (0.4–0.9)
Hypercholesterolemia					
No	7323 (86.9)	1103 (13.1)	8426	1 (ref.)	1 (ref.)
Yes	1324 (89.4)	157 (10.6)	1481	0.8 (0.7–0.9)	1.0 (0.8–1.2)
Diabetes					
No	8505 (87.2)	1246 (12.8)	9751	1 (ref.)	1 (ref.)
Yes	142 (91.0)	14 (9.0)	156	0.7 (0.4–1.2)	0.7 (0.4–1.3)
Hypertension					
No	7842 (87.3)	1141 (12.7)	8983	1 (ref.)	1 (ref.)
Yes	805 (87.1)	119 (12.9)	924	1.0 (0.8–1.2)	1.2 (1.0–1.5)
Motor vehicle accident with hospitalization					
No	8237 (87.5)	1180 (12.5)	9417	1 (ref.)	1 (ref.)
Yes	410 (83.7)	80 (16.3)	490	1.4 (1.1–1.7)	1.4 (1.1–1.9)

N/A: not applicable. *Values are numbers (percentage, calculated from total column).
[a]Adjusting simultaneously for all variables in the table but excluding 925 individuals with missing values in any variable in the table.
[b]Physical activity was categorized as sedentary if the individual reported no leisure-time physical activity, and less, moderate or very active using tertiles of MET-hours/week.

Table 2. Rate ratios (95% confidence intervals) of incident hypertension in the SUN cohort according to body mass index categories

Body mass index (kg/m^2)	< 25	25–30	> 30
Cases of HTN	76	84	20
Person-years	10219.0	2880.7	426.2
Crude RR	1 (ref.)	4.0 (2.9–5.4)	6.4 (3.9–10.5)
Adjusting for censoring using IPW[a]	1 (ref.)	4.0 (2.9–5.5)	6.7 (4.0–11.2)
Adjusting for confounding using IPW[b]	1 (ref.)	2.1 (1.5–3.0)	2.4 (1.1–5.3)
Adjusting for both confounding and selection bias using IPW[c]	1 (ref.)	2.1 (1.4–3.0)	2.4 (1.1–5.3)

HTN: hypertension; IPW: inverse probability weighting; RR: rate ratio.
[a]Adjusted for selection bias. Weights computed according to formula 2 in the text.
[b]Adjusted for age, sex, physical activity, alcohol intake, smoking, fruit and vegetable consumption, and marital status. Weights computed according to formula 1 in the text.
[c]Adjusted for age, sex, physical activity, alcohol intake, smoking, fruit and vegetable consumption, and marital status, and for selection bias. Weights computed according to formula 3 in the text.

retained in the study. In fact, non-respondents were more likely to be younger, not married, obese or overweight, smokers and to belong to the group not having a driving license. In contrast, a previous history of cardiovascular disease increased the probability of being a respondent. Finally, we show that censoring due to attrition did not introduce an important selection bias for the association between BMI and HTN when we corrected this bias using IPW.

Several reasons could explain why different variables predicted lost to follow-up in the study. Age is a factor strongly correlated with censoring in longitudinal studies. On the one hand, younger people tend to move more frequently, and that results in a greater difficulty to locate them [9, 20]. On the other hand, older age has been associated consistently with higher dropout rates in cohort studies conducted in the elderly [3, 21]. Our study population is relatively young (mean age 36 at baseline), and

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probably very mobile, causing the tracking and retention of participants more difficult through mailed questionnaires. In the Cornellá Health Interview Survey Follow-up Study (another Spanish cohort), being single was an important correlate of migration out of the study area [20], which is consistent with our results. In our study, married people had the higher retention rate.

Smoking and obesity were more frequent among participants lost to follow-up than among retained individuals. Other studies have found similar results regarding these two variables [22, 23]. Then, it can be said that health-conscious individuals have lower dropout probabilities in epidemiologic studies. The other factor associated with a higher retention rate was a previous history of cardiovascular disease. Probably, the experience of having been diagnosed of a cardiovascular disease causes these individuals to be more health conscious than the rest of the cohort, and more willing to keep participating in the cohort.

Finally, a higher educational level is one of the strongest and more consistent predictors for retention in cohort studies [9, 20, 22, 23]. In fact, this is one of the reasons to explain the decision to restrict the SUN study to university graduates. Interestingly, the retention in the cohort was similar for those with a postgraduate degree (master, PhD) than for those who had attained only a college degree.

Different methods to correct for selection bias due to differential retention have been proposed, mainly based on imputation methods for lost to follow-up individuals [24]. In this study, we have used IPW as a method to adjust both for confounding and selection bias. The use of IPW allows the estimation of causal effect under the assumption of unmeasured confounding and unmeasured informative censoring. To compute weights, we have taken into consideration the main risk factors for HTN that could act as confounding factors [25], and we can therefore be confident on the appropriateness of both assumptions.

Adjustment for confounding using IPW is not enough to remove selection bias caused by dropouts (although a traditional multivariate analysis would be sufficient in some cases). This is because in the pseudopopulation created applying weights to adjust for confounding (formula 1), there would not be any association between the potential confounders included in the IPW calculations and the exposure of interest but the possible association between those variables and censoring status, and the selection bias it causes, would remain. Therefore, additional IPWs are needed to take into account both censoring and confounding [4].

Finally, although we found no apparent selection bias for the association between BMI and HTN, or between age and HTN, we cannot be sure that these results can be generalized to other outcomes and exposures. In fact, some factors affecting probability of retention could be independent of the incidence of HTN (and then would not create selection bias), but they might be associated with another outcome. In that case, weight calculations for IPW adjustment should include that factor. In general, decisions to include or not a given factor in any weight calculation should be based in a priori subject matter knowledge [26]. Overall, study of selection bias due to censoring should be performed for each particular instance of an exposure–outcome relationship.

In conclusion, we show that the follow-up through mailed questionnaires of a geographically disperse cohort in Spain is possible. There are differences between retained participants and individuals lost to follow-up, but this does not necessarily have an important impact in the rate ratio estimates.

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